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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket 2003P-0315: CollaGenex Pharmaceuticals, Inc. Citizen Petition and Petition for Stay of Action re: Mutual Pharmaceutical Company, Inc. ANDA 65-134 (doxycycline hyclate 20 mg tablets)

Comments Opposing CollaGenex's Citizen Petition and Petition for a Stay of Action

Mutual Pharmaceutical Company, Inc. and United Research Laboratories, Inc. (collectively, "Mutual") submit these comments in opposition to CollaGenex Pharmaceuticals, Inc.'s ("CollaGenex") Citizen Petition ("Citizen Petition") and subsequently filed Petition for Stay of Action (FDA Docket No. 2003P-0315). Mutual opposes CollaGenex's petitions because they are frivolous and factually flawed.

Summary

CollaGenex's Citizen Petition fails to provide any sound, scientific justification for withholding approval of Mutual's ANDA for doxycycline hyclate tablets 20 mg ("doxycycline product"). CollaGenex asserts—without factual support—that Mutual's bioequivalency study is somehow biased because Mutual did not conduct its study in both men and women.[1] CollaGenex is wrong.

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[1] CollaGenex bases its assertions on one biostudy that Mutual submitted to the New Jersey Drug Utilization Review Council ("NJ Formulary") for the purpose of inclusion on the NJ Formulary.

CollaGenex completely ignores the fact that Mutual's proposed doxycycline product meets FDA's bioequivalence limit of 80.00 to 125.00% for the bioavailability measurements and is thus, bioequivalent to PerioStat® tablets, 20 mg ("Periostat®").

CollaGenex's contention that Periostat® is a narrow therapeutic drug that requires *in vivo* testing in women is also without merit. Periostat® fails to satisfy the definition of a drug having a narrow therapeutic range, and there is nothing in the Periostat® labeling to suggest otherwise. Moreover, even if Periostat® were a narrow therapeutic drug, Mutual still meets its burden of showing bioequivalence.

CollaGenex's petitions should be seen for what they are — a thinly veiled attempt to delay generic competition on Periostat®. CollaGenex is not pursuing these petitions in good faith. Instead, it is pursuing these petitions as part of an all-out effort to preserve its Periostat® monopoly. And that pursuit is certainly not in the public's interest.

Accordingly, FDA should deny CollaGenex's Citizen Petition because it fails to provide any legal or factual support for withholding Mutual's ANDA approval.

I. CollaGenex's Citizen Petition Should Be Denied Because Mutual's Study Satisfies Both the Statutory and Regulatory Requirements for Establishing Bioequivalence

CollaGenex argues that there is a legal requirement for including women in a bioequivalence study. (CollaGenex Petition at 4). But CollaGenex is wrong. Instead, there is guidance that recommends but does not require—including women in *in vivo* studies. (March 2003 "Guidance for Industry [on] Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations" ("2003 Biostudy Guidance")). And that

guidance issued approximately **one year after** Mutual conducted its bioequivalence study. At the time Mutual conducted its study, it was standard practice to use men.

More importantly, the 2003 Biostudy Guidance recommendation does not change the fact that Mutual's bioequivalence study satisfies the statutory and regulatory requirements for establishing that its proposed doxycycline product is bioequivalent to Periostat®. Specifically, Mutual's *in vivo* bioequivalence study demonstrates that there are no significant differences between its proposed doxycycline product and Periostat®. CollaGenex's assertion to the contrary is baseless.

Under the Federal Food, Drug, and Cosmetic Act ("FD&C Act"), an ANDA must contain "information to show that the new drug is bioequivalent to the listed drug." 21 U.S.C. § 355(j)(2)(A)(iv). According to FDA's regulations, two drugs are bioequivalent if they are "pharmaceutical equivalents or pharmaceutical equivalents whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the active moiety under similar experimental conditions...." 21 C.F.R. § 314.23(b). FDA defines a significant difference as one that is outside the 80% to 125% limit for the C_{max} (the measure of the rate of absorption) and AUC (the measure of the extent of absorption) bioavailability measures. (2003 Biostudy Guidance at 20, 23).

Mutual's *in vivo* bioequivalence study demonstrates that the rate and extent of absorption of its proposed doxycycline product do not differ significantly from the rate and extent of absorption of Periostat® when the two products are measured under similar conditions. Mutual's doxycycline AUC measurement of 95.65-112.4 and C_{max} measurement of 97.92-120.39

fall well within FDA's 80-125% limit for bioavailability measurements. (CollaGenex Petition, Ex. B, Section I at 4).

Apparently, FDA agreed with Mutual's bioequivalence assessment because on January 15, 2003, it told Mutual that the Division of Bioequivalence had completed its review and had no further questions at that time. Shortly thereafter, Mutual received verbal confirmation that its ANDA was approvable pending the resolution of an undisclosed legal issue.[2] That legal issue was supposed to have been resolved by the end of June 2003. Nonetheless, CollaGenex's legal maneuvering and flurry of petitions, such as the frivolous one here, have succeeded in delaying Mutual's otherwise approvable doxycycline ANDA.

A. CollaGenex's Citizen Petition Should Be Denied Because Mutual's Doxycycline Product Is Bioequivalent to Periostat®

CollaGenex asserts — wrongly — that Mutual's *in vivo* bioequivalence study design "systematically reduced the variability in observed pharmacokinetic responses by excluding females." (CollaGenex Petition, at 3) CollaGenex bases that assertion on its own bioequivalence study conducted in men and women. (*Id.*; Gonźales Decl. ¶¶ 6 & 9). That study compared CollaGenex's Periostat® capsules to Periostat® tablets. *Id.* Because the Periostat® tablet product exhibited higher variability (coefficient of variance or "CV") in the C_{max} and AUC measurements in CollaGenex's study than in Mutual's study, CollaGenex argues that Mutual's study results are "biased" and "suspect." (CollaGenex Petition at 3 - 4). The only thing suspect here is CollaGenex's argument.

[2] Based on recent developments, it now appears that the undisclosed legal issue was CollaGenex's request to reclassify Periostat® as a non-antibiotic drug.

B. Human Subject Variability Does Not Create A Significant Difference Between Mutual's Doxycycline Product and Periostat®

CollaGenex attempts to compare apples to oranges in an effort to create a bioequivalence issue where none exists. Mutual's *in vivo* bioequivalence data demonstrate that there are no significant differences between Mutual's product and Periostat® when accounting for subject variability. The cross-over study comparison that CollaGenex uses to support its argument is not nearly as accurate as comparing the variability of the two products under the same test conditions. Mutual's study did just that.

In Mutual's study, the CV values for the C_{max} of CollaGenex's Periostat® and Mutual's doxycycline were 26.65% and 25.74%, respectively, while the CV values for the AUC_{inf} of CollaGenex's Periostat® and Mutual's doxycycline were 25.56% and 24.53%, respectively. (CollaGenex Petition, Ex. B, Section III, Statistics at 11-12). These numbers demonstrate that there is no significant difference between Mutual's and CollaGenex's products when accounting for subject variability. *See* 21 C.F.R. § 320.23(a)(2).

Moreover, FDA's regulations do not require that an ANDA product's subject variability match that of the listed drug. In other words, Mutual's doxycycline product is bioequivalent even if it does not match Periostat®'s more highly variable formulation.

C. CollaGenex's Periostat® Labeling Demonstrates That There Is No Significant Pharmacokinetic Differences Between Genders

CollaGenex's assertion that bioequivalence studies must be conducted in both men and women because of their different pharmacokinetics is contradicted by its own Periostat® labeling. (CollaGenex Petition at 3). Periostat®'s labeling under "Gender" states: "While

female subjects had a higher rate (C_{max}) and extent of absorption (AUC), these differences are thought to be due to differences in body weight/lean body mass. Differences in other pharmacokinetic parameters were not significant." (Ex. 1, Periostat® Package Insert, "Gender").

Moreover, the cited reference supporting this labeled conclusion states: "There do not seem to be any sex-related modifications in the pharmacokinetic parameters of doxycycline." (Ex. 2, S. Saivain and G. Houin, *Clinical Pharmacokinetics of Doxycycline and Minocycline*, Clin. Pharmacokinetics 1988 at 362).

Even FDA's medical reviewers concluded that there is no appreciable pharmacokinetic difference between male and female patients. In response to CollaGenex's discussion of the pharmacokinetic parameters for males and females, the reviewer said:

> [CollaGenex] did not report individual or mean weight of the male and female patients. Given that mean female weight is $1/3^{rd}$ less than mean male weight, a weight normalized analysis of the individual pharmacokinetics [sic] parameters could have eliminated the observed differences in pharmacokinetic parameters between male and female subpopulation . . . Though AUC and C_{max} were higher in females than in males, the extent of the difference does not call for recommendation for any dose adjustment . . . Comments pertaining to gender differences in the subheading ***Gender*** under **Clinical Pharmacology** labeling should be eliminated.

(Ex. 3, 9/25/00 Pharmacology Review, Periostat Tablets at 7) (emphasis in original). In essence, CollaGenex failed to properly account for its own studies' subject variability because it ignored the patients' weights. Instead, it simply attributed the observed differences to gender. *See* 21 C.F.R. § 320.23(a)(2).

II. CollaGenex's Alleged Safety Concern Is Factually Flawed and Without Merit Because Periostat® Is an Antibiotic Without a Narrow Therapeutic Range

CollaGenex's petition erroneously asserts that: "Periostat is not an antibiotic;" Periostat "has a narrow therapeutic range;" and Periostat's doxycycline "does not reach the serum concentration associated with antibiotic action." (CollaGenex Petition at 4). Based on these faulty assertions, CollaGenex then argues that without bioequivalence studies in women, one cannot discount "the possibility" that Mutual's product "might" result in antibiotic serum concentration. *Id.* at 4. Thus, CollaGenex contends that Mutual's product may pose an increased risk of antibacterial resistance based on doxycycline's purported higher rate and extent of absorption in women. *Id.* CollaGenex's argument is factually flawed and without merit.

First, CollaGenex's Periostat® is an antibiotic. Its own clinical studies demonstrate that fact. Second, Periostat® does not have a narrow therapeutic range because it is not a drug where "the tolerance to the drug is so narrow that too small a dose can be useless and too large a dose can be dangerous to the patient's health." *In re Warfarin Sodium Antitrust Litigation*, 212 F.R.D. 231, 256 n.22 (D. Del. 2002). And third, even if Periostat® were a narrow therapeutic drug, Mutual still meets its burden for demonstrating bioequivalence.

A. Periostat® is an Antibiotic

Periostat® is an antibiotic. The *United States Pharmacopeia's* ("USP") standard for microbial action is 0.1 μg/ml with the reference test microorganism, *Staphylococcus aureus*. (Ex. 4, 2003 USP26/NF21, General Chapter <81>, 2016, 2020). CollaGenex's labeling indicates that Periostat® results in doxycycline blood serum levels of 0.79 +/- 0.285 μg/ml, well above the

0.1 μg/ml USP level for microbial action. (Ex. 1, Periostat® Package Insert) Moreover, CollaGenex's data demonstrate that almost one-quarter (23%) of its subjects from three studies maintained levels of doxycycline that exceeded ten times this amount (1 μg/ml) even before the margin of error is taken into account. (Ex. 5, 5/15/97 FDA Clinical Microbiology Review, Periostat Capsules at 7).

Thus, CollaGenex's own Periostat® labeling and clinical data show Periostat® satisfies the definition of an antibiotic.

B. Periostat® Does Not Exhibit a Narrow Therapeutic Range

Periostat® is not a drug that has a "narrow therapeutic range." According to FDA's regulations, drug products with a "narrow therapeutic ratio" are products where "there is less than a 2-fold difference in the median lethal dose (LD_{50}) and median effective dose (ED_{50}), or have less than a 2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood, and safe and effective use of the drug products requires careful dosage titration and patient monitoring." 21 C.F.R. § 320.33(c). Succinctly stated, a narrow therapeutic drug is one where "the tolerance to the drug is so narrow that too small a dose can be useless and too large a dose can be dangerous to the patient's health." *See In re Warfarin Sodium Antitrust Litigation,* 212 F.R.D. at 256 n.2.

FDA's guidances further define a "narrow therapeutic range" drug product as one where: (1) the product labeling indicates a narrow therapeutic range, (2) the drug product requires a minimum drug concentration for effectiveness, and (3) the drug requires pharmacodynamic

monitoring for its safe and intended use. (*See, e.g.*, Biowaiver Guidance at 9). Periostat® fails to satisfy this definition.

1. Periostat®'s Labeling Fails to Indicate that the Drug Has a Narrow Therapeutic Range or Other Special Dosing Instructions

Periostat®'s labeling does not contain special dosing information for obtaining therapeutic drug concentrations in its intended adult populations. Contrast this with warfarin sodium, where the product package insert notes:

> It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. Coumadin (Warfarin Sodium), a **narrow therapeutic range (index) drug**, may be affected by factors such as other drugs and dietary Vitamin K. Dosage should be controlled by periodic determinations of PT/INR or other suitable coagulation tests.

(Ex. 6, Coumadin package insert, "Warnings") (emphasis added).

Moreover, FDA's medical reviewer did not request any dose adjustment for male and female patients, or patients with different weights, for Periostat®. (Ex. 3, 9/25/00, Pharmacology Review, Periostat Tablets at 7). In fact, this reviewer requested that CollaGenex **remove any labeling that might suggest a difference between dosing male and female patients**. *Id.* That request completely contradicts CollaGenex's assertion that Periostat® has a narrow therapeutic range.

2. Periostat® Does Not Require Pharmacodynamic Monitoring

Finally, Periostat® requires no more pharmacodynamic monitoring than other doxycycline products at higher dosage strengths. FDA's microbiology reviewer noted that: "The use of low-dose tetracycline [as in Periostat®] while having a potential to bring about

populations of bacteria resistant to tetracyclines as well as other antimicrobials and to cause alterations in the microflora of the gastrointestinal tract presents **no more of potential health threat then [sic] the use of tetracyclines at higher doses** for the treatment of bacterial infections." (Ex. 5, 5/15/97, Clinical Microbiology Review, Periostat Capsules at 2) (emphasis added). Thus, even generic products with slightly higher antibiotic serum concentrations would unlikely have an increased risk of creating antibacterial resistance.

Accordingly, CollaGenex suggestion that Mutual's product will somehow present dosing concerns in women based on higher antibiotic serum concentrations is completely without merit.

C. The Bioequivalence Requirements Are the Same for Narrow Therapeutic Drugs

Even if Periostat® is considered a narrow therapeutic drug, that conclusion does not alter the fact that Mutual met its burden of showing bioequivalence. The requirements for establishing bioequivalence for narrow therapeutic drugs are no different than those for other drug products. (2003 Biostudy Guidance at 20). While some have tried to change those requirements, FDA's position remains unchanged.

In fact, certain groups and individuals have appeared before state legislatures, state boards of pharmacy and drug utilization committees to express concern for the interchangeability of generic drugs for brand drugs with narrow therapeutic ranges. Nonetheless, FDA responded by repeatedly confirming that there is no need for a more stringent criterion for narrow therapeutic range drugs than the present 90% confidence interval for the ratio of the test product *i.e.*, AUC to that of the branded drug must lie within the .80 to 1.25 for any drug or drug class (*i.e.*, 80 – 125

percent log transformed data). (*See* Ex. 7, 4/16/97 Response to National Association of Boards of Pharmacy at 1; 2003 Biostudy Guidance at 20).

Thus, regardless of Periostat®'s status as a narrow therapeutic drug, Mutual's *in vivo* studies satisfy FDA's bioequivalence requirements. The FDA should therefore deny CollaGenex's Citizen Petition.

III. FDA Should Deny CollaGenex's Petition for Stay of Action Because CollaGenex Will Not Suffer Irreparable Injury If Mutual's ANDA Is Approved and Its Citizen Petition Is Not Only Frivolous But Also Is Contrary Public Policy and Public Interest

CollaGenex fails to meet its burden for demonstrating that the Commissioner should grant a stay of action pending a decision on CollaGenex's Citizen Petition. To grant a stay, CollaGenex must demonstrate that **all** of the following elements apply:

1. Petitioner will otherwise suffer irreparable injury;
2. Petitioner's case is not frivolous and is being pursued in good faith;
3. Petitioner has demonstrated sound public policy grounds supporting the stay; and
4. Delay resulting from the stay is not outweighed by public health or other public interests.

21 C.F.R. § 10.35(e); *see Henley v. FDA*, 873 F. Supp. 776, 780 (E.D.N.Y. 1995).

A. CollaGenex Is Not Entitled to a Stay Because CollaGenex Fails to Demonstrate That It Will Suffer Irreparable Injury

CollaGenex will not suffer irreparable injury if its petition for a stay is denied. CollaGenex's primary allegations of injury are the diminution of revenues and loss of market share. (CollaGenex Petition for Stay of Action ("Stay of Action Petition") at 2–3). CollaGenex already obtained a preliminary injunction that prevents the FDA from approving Mutual's

ANDA. *See CollaGenex Pharm., Inc. v. Thompson* No. 1:03-CV-01405-RMC, Order at 1-2 (D.D.C. July 22, 2003).

Moreover, CollaGenex's allegation that "there is no mechanism by which sales and market share lost to generic products can be recovered" is incorrect. (Stay of Action Petition at 3). CollaGenex already sued Mutual and West-ward Pharmaceutical, Inc. for allegedly infringing certain patents that purport to cover Periostat®.[3] CollaGenex may recover its losses in its infringement actions, if Mutual or West-ward is found to infringe those patents.

B. CollaGenex Is Not Entitled to a Stay of Action Because CollaGenex Did Not Submit Its Citizen Petition in Good Faith

CollaGenex's petition for a stay of action should be denied because the sole purpose of CollaGenex's Citizen Petition is to delay generic competition on Periostat®. CollaGenex's petition misconstrues the legal standards of bioequivalence and supports its assertions with objectively inaccurate facts that contradict Periostat®'s labeling. CollaGenex is trying to defend its Periostat® franchise at all costs so that it can maintain its monopoly pricing.

Indeed, CollaGenex's actions prompted Mutual to file a suit in the Eastern District of Pennsylvania outlining CollaGenex's scheme to maintain its monopoly of 20 mg doxycycline hyclate, including providing misleading and false information to FDA and the U.S. District Courts.[4] CollaGenex used similar tactics against a pharmacy compounding doxycycline hyclate[5] and another company seeking generic approval for Periostat® capsules.[6] CollaGenex has

[3] *See CollaGenex Pharm., Inc. v. Mutual,* No. CV-03-3322 (E.D.N.Y. filed July 8, 2003); *CollaGenex Pharm., v. West-ward Pharm. Corp.,* No. CV-02-6094 (E.D.N.Y. filed Nov. 18, 2002).
[4] *Mutual v. CollaGenex Pharm., Inc.,* No. 03-CV-4042 (E.D. Pa. filed Jul. 9, 2003).
[5] *CollaGenex Pharm., Inc. v. Thrifty Pharm. III, Inc.* No. Civ-00-1651 (W.D. Okla. filed Sept. 25, 2000)
[6] West-ward Pharmaceuticals (Citizen Petition and Stay of Action FDA Docket No. 02P-0312).

continued to use deceptive practices to maintain its monopoly, including keeping this Citizen Petition (2003P-0315) secret from the Court during oral argument on its motion for a preliminary injunction so as to not weaken its "imminent harm" allegation. FDA should deny CollaGenex's petitions so as not to reward CollaGenex for its deceptive practices.

C. CollaGenex's Petition for a Stay of Action Should Be Denied Because CollaGenex Fails to Demonstrate Sound Policy Grounds for Supporting That Stay

There is no sound policy ground to support granting an administrative stay from approving Mutual's ANDA because that ANDA cannot be approved until the U.S. District Court for the District of Columbia dissolves the preliminary injunction that prevents the FDA from taking such action.

D. CollaGenex's Petition for a Stay of Action Should Be Denied Because CollaGenex Fails to Demonstrate That The Stay Benefits Public Health or Other Health Interests

Staying the approval of Mutual's ANDA will only provide CollaGenex with additional monopoly profits for Periostat®. It will not serve the public interest. The public benefits when lower cost, generic products are available as alternatives to branded products in the market.

Moreover, while not endangering the public health, granting CollaGenex's Stay of Action Petition will still harm the public. By granting a stay, the FDA encourages brand-name drug companies to use the petition process as a mechanism for delaying generic drug approval. The Federal Trade Commission already raised concerns regarding such anticompetitive tactics. *See* Comment on the Staff of the Bureau of Competition and of Policy Planning of the Federal Trade Commission, FDA Docket No. 99N-2497 (Mar. 2, 2000).

FDA should pay particular attention to these delay tactics when a brand company, such as CollaGenex, uses them to consistently delay generic drug approval. The instant petition is not the first time that CollaGenex tried to delay competition on Periostat®. In another petition, CollaGenex tried to raise purported safety and efficacy concerns regarding the approval a generic capsule version of Periostat®. (Ex. 8, 7/10/02 Citizen Petition at 1-2). There, CollaGenex argued that FDA cannot approve a generic capsule version until it determines that CollaGenex's own Periostat® capsules were not withdrawn from the market for safety and/or efficacy reasons. *Id.* CollaGenex made this argument notwithstanding the fact that it switched from capsule to tablet forms solely for marketing reasons and simply conducted a bioequivalence study to support that switch. (Ex. 9, 2/5/01 CollaGenex Press Release at 1).

Conclusion

Mutual believes that FDA has already determined that Mutual's proposed doxycycline product that is the subject of ANDA No. 65-134 is bioequivalent to Periostat®. Accordingly, for all the reasons stated above, the FDA should deny CollaGenex's Citizen Petition and Stay of Action Petition.

Sincerely,

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Counsel for Mutual Pharmaceutical, Inc. & United Research Laboratories, Inc.

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